PT

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/853,427	05/10/2001	James Mullin	MUL01-NP001	6770

110 7590 06/10/2004

DANN, DORFMAN, HERRELL & SKILLMAN
1601 MARKET STREET
SUITE 2400
PHILADELPHIA, PA 19103-2307

EXAMINER	
UNGAR, SUSAN NMN	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 06/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/853,427	MULLIN ET AL.	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *07 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *3,4,6-9 and 13-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) *13-15* is/are allowed.

6)☐ Claim(s) *3,4,6-9, 16-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. The Amendment filed April 7, 2004 in Response to the Office Action mailed January 4, 2004 is acknowledged and has been entered. Previously pending claims 3, 4, 7, 8, have been amended and new claims 13-17 have been added. Claims 3-4, 6-9, 13-17 are currently being examined.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The following rejections are maintained:

Claim Rejections - 35 USC § 112

4. Claims 3-4, 6-9 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in the Paper mailed January 4, 2004, Section 5, pages 4-6.

Applicant argues that it was known that mannitol could be administered to a patient by ingestion and detected in urine in order to identify intestinal permeability. Applicant points specifically to Smecuol et al (Am. J. Gastroen, 1999, 94:3547-3552) pages 4537 and 3548 to demonstrate what was known in the art.

The argument has been considered but has not been found persuasive, a review of Smecuole et al clearly discloses that the use of mannitol in the Smecuol et al is not commensurate in scope with the claimed invention. In particular, as disclosed on page 3547, mannitol was used in combination with lactulose and it was the ratio of lactulose to mannitol (lac/man) that was used for family screening for intestinal permeability (col 2). Further, Smecuole et al were specifically testing the screening value of the lactulose/mannitol ratio identification of intestinal permeability because the use of that ratio was not predictable in the art given that two research groups had suggested that the lac/man was useful for family

screening while a third had found normal intestinal permeability in a high number of new patients screened from the general population using the lac/man ratio (p. 3548, col 1). Although the reference demonstrated that the lac/man ratio could be used to detect small intestine permeability, the use of the ratio, instead of mannose alone, given that sucrose alone was used, suggests that mannose alone is not useful for identifying intestinal permeability. Given the above, it cannot be predicted that mannose alone would be useful in a method of diagnosing/screening for Barretts esophagus. The arguments have been considered but have not been found persuasive and the rejection is maintained.

5. Claims 8-9 remain rejected and new claims 16-17 are rejected under 35 USC 112, first paragraph for the reasons previously set forth in the Paper mailed January 4, 2004, Section 7, pages 9-13.

Applicant agrees that *in vitro* assays do not fully duplicate the complex conditions of the *in vivo* environment and argues that the invention as claimed in claims 8 and 9 relates to cells that have been removed from the complex *in vivo* environment. Applicant further argues that Examiner's characterization that no skilled artisan would "believe it more likely than not' that *in vitro* effects would be seen *in vivo* is inaccurate since if such an assertion is true, then all cell culture work would cease to be performed because it would be deemed wholly irrelevant. The arguments have been considered but have not been found persuasive because the issue raised here is not drawn to whether or not primary tumor tissues will be assayed when practicing the invention but rather that the support for the claimed invention is based solely on cell culture data which is understood by those of ordinary skill in the art to be unpredictable for the reasons previously set forth. The unpredictability of cell culture data in the absence of objective evidence

derived from primary tissues is acknowledged by the specification as originally filed. Although the specification clearly reports the cell culture data drawn to occludin phosphorylation on page 11, the specification teaches on page 15 that "assay of biopsy tissue will enable determination of whether or not the occludin expression and/or phosphorylation state is altered in precancerous tissue of the esophagus ..... as a correlate to changes in TJ permeability in the precancerous state". Given the teaching in the specification, given what was known in the art at the time the invention was made drawn to the unpredictability of correlating cell culture data to the *in vivo* state, no one of skill in the art would believe it more likely than not (including the instant inventors) that the invention would function as claimed based only on cell culture data, in the absence of objective evidence.

Applicant further argues that it is improper to conclude that a disclosure is not enabling based on the analysis of only one of the Wands Factors and any conclusion of nonenablement must be based on the evidence as a whole. Applicant argues that the claims are not particularly broad, artisans in the relevant field are highly skilled and the field is predictable. *In vitro* assays are known and taught in the specification.

The argument has been considered but has not been found persuasive, although Applicant is correct when stating that the claims are not particularly broad and that artisans in the relevant field are highly skilled, contrary to applicant's arguments, it is clear that the field is not predictable for the reasons previously set forth and in particular because of the teachings in the specification set forth previously and above. Although *in vitro* assays are known, it appears that Applicant is essentially inviting the artisan to determine whether or not there is a

functional use for the claimed invention by following the directions supplied on page 15. This is not sufficient to enable the claimed invention.

Applicant submits objective evidence to demonstrate that at the time the invention was made, *in vitro* data and *in vivo* results had established a correlation between occludin phosphorylation and tight junction integrity. In particular, Applicant points to Clarke et al, cited in the instant application at page 11, line 8, wherein the reference at page 3188 teaches that the phosphorylation of occludin had been studied *in vivo*. The argument has been considered but has not been found persuasive because the submitted evidence is not commensurate in scope with the claimed invention. Nothing in the Clarke et al reference reveals that occludin phosphorylation is reduced in leaky junctions. As particularly stated in the specification, "assay of biopsy tissue will enable determination of whether or not the occludin expression and/or phosphorylation state is altered in precancerous tissue of the esophagus ..... as a correlate to changes in TJ permeability in the precancerous state". The Clarke reference sheds no light on this issue.

Applicant submits objective evidence demonstrating that at the time the invention was made, *in vitro* data and *in vivo* results had established a correlation between occludin phosphorylation and tight junction integrity. In particular Applicant points to Sakakibara et al (J. Cell Biol., 1997, 137:1393-1401) which teaches that the phosphorylated occludin is "selectively concentrated at the tight junction" in biopsies of chick intestinal epithelial cells at pages 1397 and in Figure 8). The argument has been considered but has not been found persuasive because the submitted evidence is not commensurate in scope with the claimed invention. Nothing in the Sakakibara et al reference reveals that occludin phosphorylation is reduced in leaky junctions. As particularly stated in the specification, "assay of

biopsy tissue will enable determination of whether or not the occludin expression and/or phosphorylation state is altered in precancerous tissue of the esophagus ..... as a correlate to changes in TJ permeability in the precancerous state". The Sakakibara et al reference sheds no light on this issue. Further, the teaching in Sakakibara et al is drawn to a chick model. Even if the reference were to show a reduction in phosphorylation of occludin, it is not clear that a nexus could be made between the chick model and man. In particular, given the fact that the antibodies used for the chick assay do not even recognize mammalian occludin (p. 1397, col 2), it is clear that occludin in chicken and man have different structures and given differences in structure, differences in function would be expected.

Applicant further argues that Gottardi et al (PNAS,1996, 93:10779-10784) specifically teaches that ZO-1 is predominantly localized to the tight junctions of intestinal epithelial cells present in a tissue section obtained from a dog (Figure 5) and that there is a weaker nuclear staining of ZO-1 in cells that are exfoliating and no longer extensively involved in the formation of tight junctions. The argument has been considered but has not been found persuasive because the submitted evidence is not commensurate in scope with the claimed invention. Nothing in the Gottardi et al reference reveals that ZO-1 expression is reduced in the cells, but rather the reference specifically shows ZO-1 was translocated within some of the cells at the tip of the villus. In addition, a reading of the reference did not reveal that there is a weaker staining of ZO-1 in the nucleus but rather that ZO-1 is detected in outer villus epithelial cells and that nuclear ZO-1 can only be detected in cells along, approximately, the outer one-fourth of the villus. The reference provides no nexus between cells that are dying/exfoliating and cells that are

precancerous and undergoing carcinogenesis such as those cells found in Barrett's esophagus.

The arguments have been considered but have not been found persuasive and the rejection is maintained.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

6. Claim 8 is rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of "the method of claim 7, wherein said TJ leakiness is correlated with altered expression levels of ZO-1" has no clear support in the specification and the claims as originally filed. Applicant points to support for the claim amendment at page 11, lines 5-6. However, a review of page 11, lines 5-6 reveals support for the intracellular TJ-associated protein ZO-1 being down-regulated. Since the specification teaches only down-regulation and the claims are drawn to "altered expression" which read on both up- and down-regulation, it is clear that the subject matter claimed in claim 8 broadens the scope of the invention as originally disclosed in the specification.

7. Claims 3-4, 6-9 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation newly added limitation of section "e) confirming the diagnosis of Barrett's esophageal condition in a patient by performing an endoscopic biopsy." has no clear support in the specification and the claims as originally filed. Applicant points to support for the newly added limitation at page page 14, line 17. However, a review of page 14 line 17 reveals support for "patients drinking a solution of sucrose....the night before their endoscopy and collect an overnight

urine sample." A further review of the specification reveals reference to diagnosing precancerous conditions by detecting backleak of signature proteins (see pages 3-4), but no indication, suggestion or guidance that the method as newly claimed was contemplated at the time the invention was filed. The subject matter now claimed in claims 3-4 and 6-9 broadens the scope of the invention as originally disclosed in the specification.

8. Claims 13-15 appear to be allowable and free of the art.

9. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

10. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at 571-272-0841. The fax phone number for this Art Unit is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 872-9306.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
June 8, 2004